Menthol Enhances Nicotine Reward-Related Behavior by Potentiating Nicotine-Induced Changes in nAChR Function, nAChR Upregulation, and DA Neuron Excitability.

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Authors: Brandon J Henderson, Teagan R Wall, Beverley M Henley, Charlene H Kim, Sheri McKinney, Henry A Lester

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Public Summary:
Understanding why the quit rate among smokers of menthol cigarettes is lower than non-menthol smokers requires identifying the neurons that are altered by nicotine, menthol, and acetylcholine. Dopaminergic (DA) neurons in the ventral tegmental area (VTA) mediate the positive reinforcing effects of nicotine. Using mouse models, we show that menthol enhances nicotine-induced changes in nicotinic acetylcholine receptors (nAChRs) expressed on midbrain DA neurons. Menthol plus nicotine upregulates nAChR number and function on midbrain DA neurons more than nicotine alone. Menthol also enhances nicotine-induced changes in DA neuron excitability. In a conditioned place preference (CPP) assay, we observed that menthol plus nicotine produces greater reward-related behavior than nicotine alone. Our results connect changes in midbrain DA neurons to menthol-induced enhancements of nicotine reward-related behavior and may help explain how smokers of menthol cigarettes exhibit reduced cessation rates.

Scientific Abstract:
Understanding why the quit rate among smokers of menthol cigarettes is lower than non-menthol smokers requires identifying the neurons that are altered by nicotine, menthol, and acetylcholine. Dopaminergic (DA) neurons in the ventral tegmental area (VTA) mediate the positive reinforcing effects of nicotine. Using mouse models, we show that menthol enhances nicotine-induced changes in nicotinic acetylcholine receptors (nAChRs) expressed on midbrain DA neurons. Menthol plus nicotine upregulates nAChR number and function on midbrain DA neurons more than nicotine alone. Menthol also enhances nicotine-induced changes in DA neuron excitability. In a conditioned place preference (CPP) assay, we observed that menthol plus nicotine produces greater reward-related behavior than nicotine alone. Our results connect changes in midbrain DA neurons to menthol-induced enhancements of nicotine reward-related behavior and may help explain how smokers of menthol cigarettes exhibit reduced cessation rates.